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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,102	07/17/2000	NICHOLAS THOMAS	PA9720	9263

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EXAMINER
GABEL, GAILENE

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/18/2002 6

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,102	THOMAS, NICHOLAS	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 4/3/02 in Paper No. 8 is acknowledged and has been entered. Claims 1-11 have been amended. Currently, claims 1-11 are pending and under examination.

Rejections Withdrawn

2. In light of Applicant's amendment and arguments, the rejection of claims 1-2, 4, 6-7, and 9-10 under 35 U.S.C. 102(e) as being anticipated by Haugland et al. (US 5,723,218), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step b) remains vague and indefinite in reciting, "dispensing each ... N populations of carrier beads into a separate corresponding one of N different vessels" because as recited, it appears that Applicant dispenses all N populations into a separate corresponding vessel, amongst N different reaction vessels which is not Applicant's intent. Perhaps, Applicant intends "dispensing each ... into separate N

different reaction vessels, each one of the reaction vessels corresponding to one of the N populations of the distinguishable populations of carrier beads".

-Same analogous comments and problems in step b) apply to the "N samples" in step c) of claim 1.

Claim 1 is incomplete and confusing. Claim 1 step d) recites "reagents for performing an assay whereby a signal moiety is partitioned between said carrier beads" so as to indicate "presence or absence of the compound to be tested, the concentration ..., and the biological activity ..." but fails to specifically and distinctly define the structural or functional cooperative relationship which exists between the "reagents", "the distinguishable populations of carrier beads", the "compounds to be tested" , and the "N samples" and how this "partition of signal moiety" is effected in a [multiplex] assay in the absence of 1) an "identifier" or a "determinant" specific for each population of carrier beads that differentially identifies between each population of carrier beads, 2) specific labeled binding reagents, i.e. labeled antibody, that provides specificity towards each different antigen and the compound's effect towards them so as to determine level of biological activity, 3) teaching of the nature of the carrier beads in relation to the reagents to differentially provide "partition of signal moiety" for each compound to be tested, 4) the nature of the sample, i.e. containing multiple analytes, a single analyte, or cell-based assay including all intracellular and cell surface antigen, and the resultant mixture so as to define and correlate between presence/absence of a compound, concentration of the compound, and biological activity, i.e. apoptotic, toxic, or modulatory activity, etc. in each of the N samples. As recited, it is unclear how or that

multiplexing involving N number of samples, having multiple analytes which are assayed using [undefined] reagents and which are responsive to effects of N number of compounds, and N distinct populations of beads, which are all dispensed into N number of different reaction vessels, then combined altogether for analysis using flow cytometry is effected. Same analogous comments and problems follow and are applicable to step f) of claim 1, claim 6, claim 9, and also claim 11.

-it is unclear what is encompassed in the recitation of "an assay". For example, how does the assay indicate presence, absence, concentration, and activity of the different compounds.

-"the assay medium" lacks antecedent support.

-it is unclear how "flow cytometric analysis" is able to "assay the signal moiety". Perhaps, Applicant intends to recite that the flow cytometric analysis encompasses "detection" of a signal moiety that determines or correlates to the presence, absence, concentration, activity, etc. of compounds which has resulted from the assay in step c), for example. Same analogous problems and comments apply to claim 4.

Applicant is requested to note that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims recited must stand on their own merit.

Claim 4 is vague and indefinite in reciting "analysis by flow cytometry to assay said signal moiety" because claims 1 and 2 from which it depends appears to have already completed the "assay".

Claim 6 is indefinite in reciting, "a reagent of the reagents recited in step d)" because it is unclear how "a reagent" in the instant claim relates with the rest of the undefined "reagents" recited in claim 1 from which it depends.

Claim 9 is ambiguous in reciting, "the signal moiety is a fluorescent dye" because it does not distinctly define how this fluorescent dye differentially and functionally provides distinction from the "fluorescent dye" in claims 1, 2, and 7 which provides for a label used in differentiating populations of carrier beads in the method.

Claim 11 is indefinite in reciting "identical", "substantially identical", and "additional, because the terms are subjective and lack a comparative basis for defining their metes and bounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-7 and 9-10 stand rejected under 35 U.S.C. 102(e) as being anticipated by Yamashita et al. (US 6,210,900) for reason of record.

Yamashita et al. disclose a method for identifying test compounds having desired characteristics and identifying essential moieties in a lead structure which comprises preparing one or more encoded combinatorial libraries from a specified set of reaction

sequences wherein the test compounds are tested for biological activity (pharmaceutical activity). Specifically, Yamashita et al. disclose providing populations of labeled (tagged) beads with fluorescently labeled identifiers attached thereto for encoding the combinatorial libraries (see Summary). Each population of beads is distinguishable from other populations by virtue of size, composition, fluorescent marker, and fluorescent label identifier. The identifier is a "coding" label attached to a population of beads by adding ratios of a fluorophore and a non-fluorophore or adding multiple different fluorophores in varying ratios (see column 3, lines 38-55). Yamashita et al. disclose that the number of readily distinguishable populations of beads correspond to the number of alternative variables in a registry. Yamashita et al. disclose dispensing an entirety of a population in a separate reaction vessel or well of a microtiter plate; beads usually are divided into populations of 1000 or more (see column 4, lines 16-37). Thereafter, appropriate reagents are added to each individual reaction vessel for reaction or assay to take place. After washing, the populations of beads are combined into a single mixture and subjected to flow cytometry for sorting (see column 4, lines 38-49). The compounds of the library can be tested using samples in a soluble receptor assay (see column 13, lines 1-7).

5. Claims 1-2, 4, 6-7, and 9-11 stand rejected under 35 U.S.C. 102(e) as being anticipated by Chandler et al. (US 5,981,180) for reason of record.

Chandler et al. disclose multiplexed analysis of samples each containing test compounds (analytes) (see column 7, lines 25-61). Chandler et al. disclose providing

populations of carrier beads (beadsets or bead subsets) labeled with an appropriate reactant such as a biomolecule or a DNA sequence (see column 7, line 63 to column 6, line 9). Each population of beads is homogeneous and differing in at least one distinguishable parameter from other populations. Distinguishable parameters include size, shape, labels which have fluorescent emissions in more than one wavelength resulting from the presence of two or fluorochromes on the beads, etc. The classification parameter for each population is known and therefore the identity of each population can be verified using flow cytometry (see column 3, line 65 to column 4). Each bead population is coated with different reactants so as to bind or react and detect different compounds. For more quantitative analysis of compounds and biological activity (kinetic studies), each population of beads may be coated with a same reactant but at different concentrations so as to produce populations varying in density of precoated reactant rather than type of reactant; thereby allowing a parameter to serve as an indicator of reactant identity or reactant density.

6. Claims 1-10 stand rejected under 35 U.S.C. 102(e) as being anticipated by Dower et al. (US 6,165,717).

Dower et al. synthesize nonporous solid supports which are carrier beads (particles) comprising a single bead or a populations of beads (two or more linked particles) for use in methods of identifying multiple compounds in samples. Each population of beads has coated, thereto, identifier tags which may have any recognizable features that carry required information that is distinguishable between each population (see column 2, line 64 to column 3, line 21). The identifier tag in each

population may be an oligonucleotide preferably composed of pyrimidines or it may be any recognizable feature that is microscopically distinguishable in size, shape, color, optical density; chemically reactive; magnetically or electronically encoded, etc. (see column 4, lines 26-38 and column 8, lines 35-50). The populations of beads are also coated with ligands that have affinity for specific compounds. Compounds or receptors which can be investigated using the carrier beads in an assay, include drugs. To synthesize oligomers, the populations of beads are apportioned in a stochastic manner among a plurality of reaction vessels, pooled, and then further apportioned and pooled again in a series of twenty times then subjecting them to flow cytometry (see columns 9-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 8 and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamashita et al. (US 6,210,900) in view of Mandecki (US 5,641,634).

Yamashita et al. has been discussed supra. Yamashita et al. differ in failing to disclose that the beads populations are electronically labeled. Yamashita et al. also differ in failing to disclose a kit.

Mandecki et al. disclose a multiplex assay using electronically encoded carrier beads (solid phase particles associated with transponders) that are assigned a unique index number which can be retrieved by a scanner device at any time during an assay for a compound. According to Mandecki et al., the carrier beads are analyzed to detect a label indicative of a reaction or binding of the compound to the carrier bead such as fluorescence, color, or radioactivity. Analysis is then preceded or followed by the decoding of the index number from the transponder. Both analysis and decoding can be done using two different instruments : a fluorimeter and a scanner. Mandecki et al. also disclose a kit for detecting biomolecular compounds in samples using carrier beads, assay vessels, coated labeled reagent (see columns 1-3).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to further electronically encode the populations of beads as disclosed by Mandecki so as to be an added "another" decipherable parameter in the bead populations in the method as taught by Yamashita because Mandecki specifically disclosed its applicability in multiplex assays. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the transponders of Mandecki into the method of Yamashita because Mandecki specifically disclosed their advantage in further detecting and differentiating increased number of analytes simultaneously in comparison to current multiplex assays.

Further, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the reagents, labels and vessels taught by Yamashita into a kit arrangement such as in the disclosure of Mandecki because test

kits are conventional and well known in the art for their recognized advantages of convenience and economy.

Response to Arguments

8. Applicant's arguments filed 4/3/02 have been fully considered but they are not persuasive.

A) Applicant argues that Yamashita does not teach use of a method for pre-existing compounds which are not coupled to beads and does not disclose the addition of samples containing a compound to be tested as recited in the claims. Applicant argues that the method of Yamashita is, therefore, not compatible with use of diverse libraries of compounds.

In response, the rejected claims, as recited, do not exclude that the compounds are coupled to the beads. The preamble recited only that the samples "contain" a compound to be tested. Further, "the addition of samples containing a compound" is not recited as a feature or limitation or method step in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

B) Applicant argues that Chandler discloses a multiplexed assay of "N analytes" in a single sample using N populations of beads, rather than "N samples" wherein "N" is

defined as "greater than 2". Applicant also argues that Chandler does not disclose use of encoded beads to identify different sample for processing in the same assay

In response, the rejected claims, as recited, are not clear or specific with regards to what is encompassed in use of the term "sample" which reads on "N analyte samples"; therefore, the rejected claims are inherently anticipated by Chandler.

In addition, the carrier beads of Chandler are indeed, encoded, using specific discriminating factors incorporated into the beads to render one population of beads distinct from another. Further, the recitation of "use of encoded beads to identify a number of different samples for processing in the same assay" is not distinctly recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

C) Applicant argues that Dower does not teach use of a method for pre-existing compounds which are not coupled to beads and that the method of Dower is not compatible with use of diverse libraries and or compounds which are not compatible with attachment to beads. Applicant further argues that Dower does not use encoded beads to identify a number of different samples for processing in the same assay.

In response, the rejected claims, as recited, do not exclude that the compounds are coupled to the beads. The preamble on recited only that the samples "contain" a compound to be tested.

In addition, the carrier beads of Dower are indeed, encoded, using identifier tags incorporated into the beads, or are magnetically or electronically encoded, to render one population of beads distinct from another. Further, the recitation of "use of encoded beads to identify a number of different samples for processing in the same assay" is not distinctly recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

D) Applicant argues that the claims differ from the references cited because it permits parallel processing of multiple samples through detection instrumentation. Applicant points to Attachment #1 to provide a comparison between prior art and the instant invention claimed.

In response, the cited references read on the claims as currently recited because the recited claims 1) do not distinctly define what is encompassed in the recitation of "N samples" which reads on "N analyte samples" or "N pharmaceutical samples", 2) do not exclude that each of the N samples contain multiple analytes.

E) Applicant argues that the combination of Mandecki with Yamashita does not render obvious the claimed invention because Mandecki fails to remedy the deficiencies of Yamashita, i.e. Yamashita does not teach use of a method with pre-existing compounds that are not coupled to beads and does not disclose the addition of samples containing a compound to be tested as recited in the claims.

In response, the rejected claims, as recited, do not exclude that the compounds are coupled to the beads. The preamble recited only that the samples "contain" a compound to be tested. Further, "the addition of samples containing a compound" is not recited as a feature or limitation or method step in the rejected claims.

In this case, Yamashita discloses a method for identifying test compounds as well as essential moieties in a lead structure which comprises preparing one or more encoded combinatorial libraries from a specified set of reaction sequences wherein the test compounds are tested for biological activity. Yamashita provides populations of labeled beads with fluorescent identifiers attached thereto for encoding the combinatorial libraries. The identifier is a "coding" label attached to each population of beads by adding ratios of a fluorophore and a non-fluorophore or adding multiple different fluorophores in varying ratios. Mandecki is incorporated for the disclosure of a multiplex assay using electronically encoded carrier beads that are assigned a unique index number which can be retrieved by a scanner device at any time during an assay for a compound.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to further electronically encode the populations of beads as disclosed by Mandecki so as to be an added "another" decipherable parameter in the bead populations in the method as taught by Yamashita because Mandecki specifically disclosed its applicability in multiplex assays. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the transponders of Mandecki into the method of Yamashita because Mandecki specifically disclosed their

advantage in further detecting and differentiating increased number of analytes in samples simultaneously, in comparison to current multiplex assays.

9. For reasons aforementioned, no claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641

Gailene R. Gabel
June 14, 2002